(12) UK Patent Application (19) GB (11) 2 160 201 A

(43) Application published 18 Dec 1985

(21) Application No 8514648

(22) Date of filing 10 Jun 1985

(30) Priority data

(31) 8415174 (32) 14 Jun 1984 (33) GB
8432091 19 Dec 1984

(51) INT CL⁴
C07D 239/94 A61K 31/635 C07D 237/28 401/10 403/10 //
(C07D 401/10 211:56 237:28 239:94) (C07D 403/10
207:09 239:94)

(52) Domestic classification
C2C 1341 1532 1592 1604 213 215 220 22Y 246 250 251
252 25Y 28X 29X 29Y 30Y 311 313 318 31Y 321 322 323
32Y 337 339 342 34Y 385 394 39Y 494 510 51X 535 537
539 60X 620 630 650 660 670 680 694 802 80Y AA RJ SF
SG
U1S 2415 C2C

(71) Applicant
John Wyeth & Brother Limited (United Kingdom),
Huntercombe Lane South, Taplow, Maidenhead,
Berkshire SL6 0PH

(72) Inventors
John Terence Arnott Boyle,
Richard Simon Todd

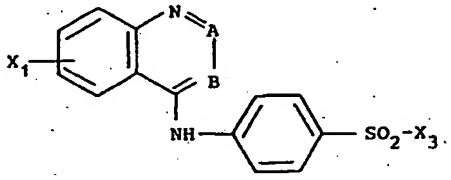
(74) Agent and/or Address for Service
G. R. Porter,
c/o Wyeth Laboratories, Patent & Trade Department,
Huntercombe Lane South, Taplow, Maidenhead,
Berkshire SL6 0PH

(56) Documents cited
None

(58) Field of search
C2C

(54) Quinazoline and cinnoline derivatives

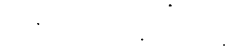
(57) Novel quinazoline and cinnoline derivatives having the formula



(I)

(wherein one of A and B is CH and the other one of A and B is N; X_1 is halogen or CF_3 and X_3 is one of the groups II, III, IV or V

$-NR_1-Q-NR_2R_3$ (II)



(III)

(IV)

(V)

where Q is lower alkylene; R_1 is hydrogen or lower alkyl; R_2 and R_3 are independently lower alkyl or R_2 and R_3 are a divalent radical such that HNR_2R_3 is a secondary cyclic amine with 5 to 7 ring atoms; R_4 is lower alkyl; n is 0 or 1; the rings shown in formulae III and IV are piperidine or pyrrolidine optionally substituted by lower alkyl; and the ring shown in formula V is piperazine optionally substituted by lower alkyl) and their pharmaceutically acceptable salts are useful as pharmaceuticals particularly as *anti-hypertensives*.

Novel intermediates are also described including the corresponding sulphonic acids of formula I (where A, B and X_1 are defined above and X_3 is OH).

Formulae in the printed specification were reproduced from drawings submitted after the date of filing, in accordance with Rule 20(14) of the Patents Rules 1982.

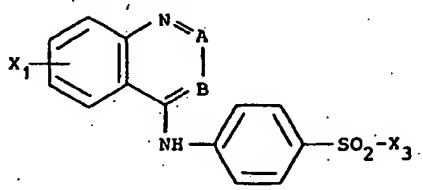
GB 2 160 201 A

SPECIFICATION

Quinazoline and cinnoline derivatives

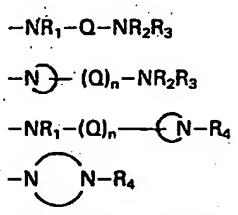
The invention relates to novel quinazoline and cinnoline derivatives that are useful as pharmaceuticals, particularly as anti-hypertensive agents. The invention also provides processes for their preparation, pharmaceutical compositions containing them, novel compounds useful as intermediates for the preparation of the said derivatives and a process for the preparation of the intermediate compounds.

The invention provides, as novel quinazoline and cinnoline derivatives, compounds having the general formula I



(I)

wherein one of A and B is CH whilst the other one of A and B is N; X_1 is halogen or trifluoromethyl and X_3 represents a group having one of formulae II, III, IV and V.



(II)

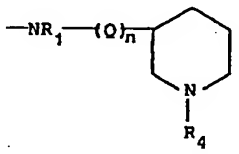
(III)

(IV)

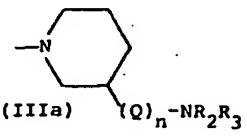
(V)

wherein Q is lower alkylene; R_1 is hydrogen or lower alkyl; R_2 and R_3 are, independently, lower alkyl or R_2 and R_3 together form a divalent radical such that R_2R_3NH is a secondary cyclic amine with 5 to 7 ring atoms; R_4 is lower alkyl; n is 0 or 1; the ring illustrated in formulae III and IV is a piperidine or pyrrolidine ring that may be substituted on one or more carbon ring members by lower alkyl and the ring illustrated in formula V is a piperazine ring that may be substituted on one or more carbon ring members by lower alkyl; and the pharmaceutically acceptable salts thereof. These compounds are indicated for pharmaceutical use, particularly as anti-hypertensive agents.

It will be apparent to those skilled in the art that the above definition of X_3 includes moieties possessing an asymmetric carbon atom especially for instance in the cases where Q is present and is a chain of 1 to 4 methylene groups, the chain being mono-substituted by methyl or ethyl or where X_3 is of formula IVa or IIIa



(IVd)

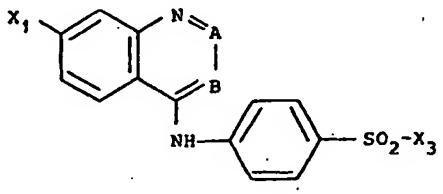


(IIIa)

It is to be understood that formula I is intended to encompass each enantiomer where the compound contains an asymmetric carbon atom and mixtures of enantiomers, for instance, a racemic mixture of enantiomers. Separation of enantiomers can be carried out using general methods known in the literature.

When A is CH whilst B is N the compounds of the invention are quinazoline derivatives. Where A is N whilst B is CH the compounds of the invention are cinnoline derivatives.

X_1 may substitute any of the 5,6,7 and 8 positions of the quinazoline or cinnoline ring system, but is preferably at the 7- or 8- position, advantageously the 7- position. Where X_1 is at the 7- position, formula I may be represented as Ia



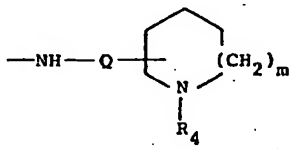
(Ia)

X_1 represents halogen, for instance chlorine or bromine, or trifluoromethyl. X_1 is preferably chlorine.

In formulae II and IV, R_1 represents hydrogen or lower alkyl (for instance methyl, ethyl, propyl, butyl). R_1 is preferably hydrogen. In formulae II, III and IV Q is lower alkylene which may be a straight chain i.e. a chain of 1 to 6, preferably 1 to 4, methylene groups. Alternatively Q may be a branched lower alkylene group, for instance, a chain of 1 to 4 methylene groups, the chain being mono- or di-substituted by methyl or monosubstituted by ethyl. R_2 and R_3 in formulae II and III, when separated, are each lower alkyl (for instance, methyl, ethyl, propyl, butyl). Alternatively R_2 and R_3 may be joined together to form a divalent radical such that R_1R_2NH is a secondary cyclic amine with 5 to 7 ring atoms, e.g. pyrrolidine, piperidine, morpholine or thiomorpholine. In this case R_1 and R_2 may together have the formula $-(CH_2)_2-X_2-(CH_2)_2-$ where X_2 is $-(CH_2)_n-$, O or S where n is 0, 1 or 2. R_2 and R_3 are preferably lower alkyl. n in formula III and IV is 0 or 1. R_4 in formula IV and V is lower alkyl (for instance, methyl, ethyl, propyl, butyl). The ring attached to $-(Q)_n-$ in formulae III and IV is a piperidine or pyrrolidine ring whose nitrogen atom is shown in the formula. The ring may be substituted on one or two ring carbon atoms by lower alkyl (for instance methyl, ethyl, propyl, butyl). The ring carbon atoms are preferably unsubstituted. The ring attached to R_4 in formula V is a piperazine ring (whose nitrogen atoms are shown in the formula). The piperazine ring may be substituted on one or two ring carbon atoms by lower alkyl (for instance methyl, ethyl, propyl, butyl), but is preferably unsubstituted.

Advantageously X_3 is a group having the formula IIa or IVa

$$-NH-Q-NR_2R_3 \qquad \text{(IIa)}$$



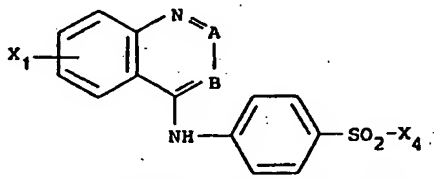
(IVa)

where Q is alkylene of 1 to 4 carbon atoms; R_2, R_3 and R_4 are, independently, alkyl of 1 to 4 carbon atoms and m is 0 or 1.

The term "lower" as used herein to refer to such groups as alkyl, alkoxy, alkanoyl and alkylene, indicates that the group contains up to 6, preferably up to 4, carbon atoms. The group may be in the form of a straight chain or may be branched.

The compounds having formula I form acid addition salts with acids. Examples of acid addition salts are those formed from inorganic and organic acids and in particular include the sulphate, hydrochloride, hydrobromide, hydroiodide, nitrate, phosphate, sulphonates (for instance the methanesulphonate or p-toluenesulphonate), acetate, maleate, fumarate, tartrate, malonate, citrate and formate.

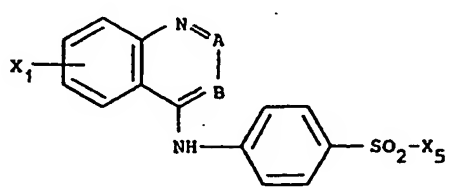
The invention also provides, as novel quinazoline and cinnoline derivatives, compounds having the general formula VI



(VI)

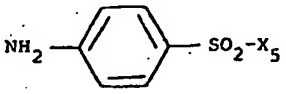
(where X_1, A and B are as defined above and X_4 is $-OH$ or $-NR_1R_5$ where R_5 is hydrogen or a group having the formula $-Q-Z$ where Q is as defined above and Z is a leaving group or atom, preferably a halogen atom or an organosulphonyloxy group, advantageously chlorine, bromine, C_1-C_6 alkanesulphonyloxy, or substituted or unsubstituted benzenesulphonyloxy, for instance, tosyloxy and R_1 is as defined above) and their salts. Such salts include acid addition salts and also sulphonate salts of the sulphonic acid where X_4 is $-OH$. The compounds having formula VI and their salts are useful as intermediates for the preparation of compounds having the formula I and their pharmaceutically acceptable acid addition salts.

A first process according to the invention is for the preparation of compounds having the formula



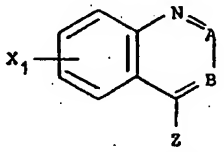
(VII)

(where A, B and X_1 are as defined above and X_5 represents X_3, $-OH$ or $-NHR_1$ where X_3 and R_1 are as defined above) or a salt thereof, wherein a compound having the formula VIII



(VIII)

(wherein X_5 is as defined above) or a salt thereof is reacted with a compound having the formula IX

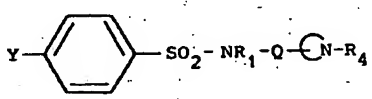


(IX)

(where X_1, A and B are as defined above and Z is a leaving group or atom, preferably a halogen atom such as iodine, bromine or chlorine) and, if desired, a compound having formula VII (where X_5 is $-OH$ or $-NHR_1$) is converted into a salt thereof or a compound having formula VII (where X_5 is X_3) is converted into a pharmaceutically acceptable salt thereof or a salt of a compound having formula VII is converted into the compound having formula VII.

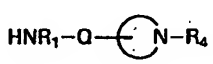
The reaction of the compounds VIII and IX can be carried out in aqueous alcohol with or without acid catalysis. The compounds of formula IX are generally known or, if new, can be prepared in known manner. The sulphonamides (VIII where X_5 is $-NHR_1$ or X_3) can be prepared by acetylating the sulphanilic acid, converting the N-(acetyl) sulphanilic acid into its sulphonyl chloride derivative, sulphonylating a compound of formula R_1NH_2 or X_3H or a salt thereof with the sulphonyl chloride and hydrolysing the sulphonylation product to give the desired aminobenzenesulphonamide. Alternatively, the preparation can be carried out by converting 4-nitrobenzenesulphonic acid into its sulphonyl chloride derivative, sulphonylating a compound of formula R_1NH_2 or X_3H or a salt thereof with the sulphonyl chloride and reducing the nitro group to give the desired aminobenzenesulphonamide.

A further class of novel intermediates according to the invention are useful for the preparation of compounds having formula I where X_3 has formula IV where n is 1. These novel intermediates have formula IVb



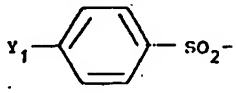
(IVb)

and their acid addition salts where Y is $-NH_2$ (amino), protected amino, for instance lower alkanoylamino, preferably acetamido, or latent amino, preferably nitro and R_1, Q, R_4 and the ring attached to R_4 have the same meanings as in formula IV. The compounds having formula IVb may be prepared by sulphonylating a compound having the formula IVc



(IVc)

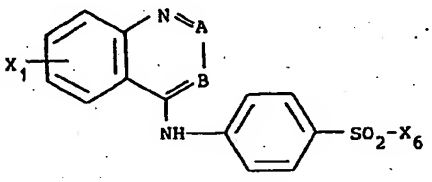
to introduce a sulphonyl group having the formula



(XXIII)

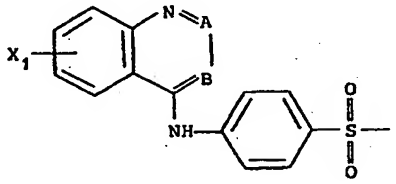
where Y_1 is protected amino or latent amino and, where Y is $-NH_2$, converting the protected amino or latent amino group Y_1 of the sulphonation product into amino, for instance, by reduction of nitro or hydrolysis of lower alkanoylamino.

The compounds obtained by the aforesaid process where R_5 is hydroxy and their salts can be used to prepare the sulphonamide intermediates and end products by forming a sulphonylating agent, preferably the sulphonyl chloride, and sulphonylating ammonia or an appropriate amine or a salt thereof. Accordingly a second process provided by this invention is for the preparation of compounds having the formula X



(X)

(where X_1, A and B are as defined above and X_6 is X_3 (as defined above) or $-NR_1R_5$ where R_1 and R_5 are as defined above) and the salts thereof. According to this process a compound of general formula X_6H (XI) where X_6 is as defined above or a salt thereof is sulphonylated to introduce the sulphonyl group of general formula XII

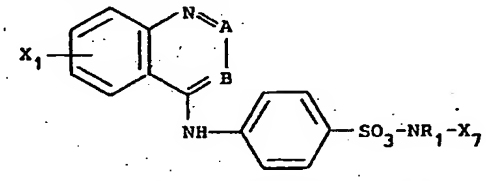


(XII)

(where X_1, A and B are as defined above) and, if desired, a compound having formula X is converted into a salt thereof or a salt of a compound having formula X is converted into the compound having formula X.

As sulphonylating agent, the sulphonyl chloride is preferably used. The reaction can be carried out in known manner for sulphonylation of ammonia and amines. The sulphonylation can be carried out in a suitable solvent, for instance, chloroform or methylene chloride, in the presence of a base to neutralise the hydrogen chloride formed. The base may be provided by using, for instance, an alkali metal carbonate or bicarbonate or a tertiary amine, for instance, triethylamine or an excess of the basic compound having formula X_6H.

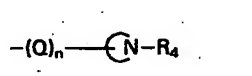
The chemical intermediate sulphonamides of the invention (formula VI where X_4 is $-NR_1R_5$) may be prepared as described above with reference to formula VII where X_5 is $-NHR_1$ or formula X where X_6 is $-NR_1R_5$. In the case where X_4 is $-NHR_1$ the sulphonamide may be converted into some of the end product sulphonamides by alkylation under basic conditions. Accordingly a third process provided by the invention is for the preparation of a compound having the general formula XIII



(XIII)

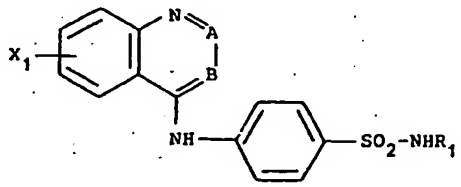
(wherein X_1, A, B and R_1 are as defined above and X_7 represents a group having the formula XIV or XV

$$-Q-NR_2R_3 \qquad \text{(XIV)}$$



(XV)

(wherein Q, n, R_2, R_3, R_4 and the ring shown in formula XV have the same meanings as defined under formulae II and (IV) or a pharmaceutically acceptable salt thereof, wherein a compound having the formula XVI

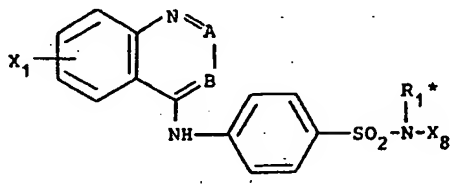


(XVI)

(where X_1, X_2, A, B and R are as defined above) is reacted with a compound having the formula $Z\text{-}X_7$ (XVII) (where Z and X_7 are as defined above) under basic conditions and, if desired, the resultant compound of formula XII is converted into pharmaceutically acceptable salt thereof.

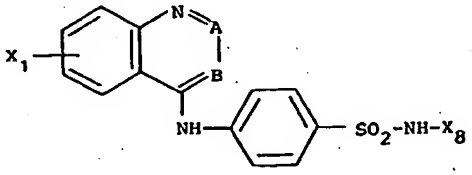
The above process may be carried out in known manner for the alkylation of sulphonamides. The product XIII may be recovered as such or as an acid addition salt by known isolation procedures.

The intermediate sulphonamides of formula VI where X_4 is $-NH_2$ and the sulphonamides of formula XIII (where R_1 is hydrogen) may also be alkylated to introduce R_1 as lower alkyl. Accordingly the invention also provides a process for the preparation of a compound having the formula XVIII



(XVIII)

(where X_1, A and B as defined above; R_1* is lower alkyl and X_8 is X_7 or hydrogen) or a salt thereof, wherein a compound having the formula XIX

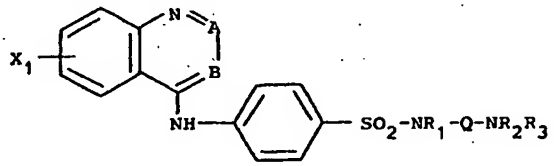


(XIX)

(wherein X_1, X_8, A and B are as defined above) is reacted with an alkylating agent under basic conditions to introduce the lower alkyl group R_1* and, if desired, the resultant compound having formula XVIII is converted into a salt thereof. This process may be carried out in accordance with known procedures for alkylation of sulphonamides. The product (XIX) may be recovered as such or as an acid addition salt by known isolation procedures.

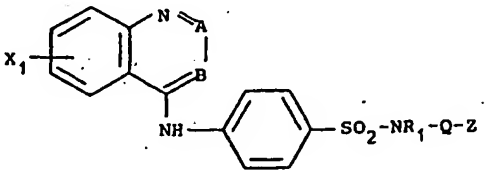
It will be apparent that the sulphonamides of formula I where X_3 is of formula II or IV in which R_1 is lower alkyl and their pharmaceutically acceptable salts can be prepared from corresponding sulphonamides whose sulphonamide nitrogen atom is unsubstituted by applying the third and fourth procedures of the invention in either order. Either one of X_7 and the lower alkyl group represented by R_1 is introduced as a first step and the other one of X_7 and the lower alkyl group is introduced as a second step.

The intermediate sulphonamides having formula VI where X_4 is $-NR_1-Q-Z$ can also be used to prepare some of the end compounds of the invention. Accordingly the invention also provides a process for the preparation of a compound having the formula



(XX)

(wherein X_1, A and B are as defined under formula I and R_1, R_2, R_3 and Q are as defined under formula II) or a pharmaceutically acceptable salt thereof, wherein a compound having the formula



(XXI)

wherein X_1, A, B, Q and R_1 are as defined under formula XX, and Z is as explained under formula VI) is reacted with a compound having the formula HNR_2R_3 (XXII) in which R_2 and R_3 are as defined under formula XX or a salt thereof and, if desired, a compound having formula XX is converted into a pharmaceutically acceptable salt thereof or a salt of a compound having formula XX is converted into a compound having

formula XX. The reaction of the compound XXI with the amine XXII can be carried out in conventional manner for the conversion of secondary amines into tertiary amines, preferably under pressure.

The novel compounds having general formula I and their pharmaceutically acceptable salts are indicated for use as anti-hypertensive agents. The compounds may be tested for their response on the blood pressure of spontaneously hypertensive rats in the following procedure:-

The blood pressure of male or female conscious rats that are spontaneously hypertensive are measured in a 39°C constant temperature housing by means of a tail cuff. Rats with systolic pressures below 155mm Hg are not used. Groups of rats (4 per group) are dosed orally with the test substance in a suitable vehicle or with vehicle alone. Systolic pressures are recorded before dosing and at selected time points afterwards (2 hours, 6 hours and 24 hours).

The following table indicates results obtained in the procedure described above:-

Compound (identified by Example No.)	*Dose (millimoles per Kg)*	*Blood pressure (as % of blood pressure before dosing)*		
		After 2 hours	*After 6 hours*	*After 24 hours*
3	0.03	80	67	102
	0.03	77	70	85
	0.015	84	75	86
	0.003	92	85	91
5	0.03	83	75	95
6	0.03	77	67	97
7	0.03	71	73	98
8	0.03	98	85	107
9	0.03	71	62	70
16b	0.03	74	58	85

The invention also provides a pharmaceutical composition comprising a compound having formula I or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical composition. In such a composition, the carrier is generally a solid or liquid or a mixture of a solid and a liquid.

Solid form compositions include powders, granules, tablets, capsules (e.g. hard and soft gelatin capsules), suppositories and pessaries. A solid carrier can be, for example, one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, fillers, glidants, compression aides, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99%, e.g. from 0.03 to 99%, preferably 1 to 80% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by the carrier, which is thus in association with it. Similarly cachets are included.

Liquid form compositions include, for example, solutions, suspensions, emulsions, syrups, elixirs and pressurised compositions. The active ingredient, for example, can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilisers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycerol and glycols) and their derivatives and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. When the compound is orally active it can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containign liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form. The quantity of the active ingredient in unit dose of composition may be varied or adjusted from 0.5 mg or less to 750 mg or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of the carrier where the compounds are in unit dosage form.

The invention is illustrated by the following examples:-

EXAMPLE 1

4-(7-Chloro-4-quinazolinylamino)benzenesulphonic acid

Sulphanilic acid (12.1g, 0.07 mole) was partly dissolved in 280 millilitres of aqueous ethanol (50% by volume) at reflux and 4,7-dichloroquinazoline (13.9g, 0.07 mole) was added rapidly in a few portions. The mixture was refluxed for a further 15 minutes, cooled and filtered to give the title compound hemihydrate of melting point greater than 300°C.

Analysis:

Calculated for $C_{14}H_{10}ClN_3O_3S.\frac{1}{2}H_2O$: C, 48.8%; H, 3.22%; N, 12.2%

Found: C, 48.7%, H, 3.32%; N, 11.8%

The sulphonyl chloride hydrochloride derivative of the title compound may be prepared by the following procedure. The title compound (12.6g, 0.036 mole) was heated to reflux for 4 hours in thionyl chloride (90ml) containing dimethylformamide (0.75ml). Excess thionyl chloride was evaporated under reduced pressure and the solid was washed with toluene to give the sulphonyl chloride hydrochloride (13.9g).

EXAMPLE 2

4-(7-Chloro-4-cinnolinylamino)benzenesulphonic acid

Sulphanilic acid (1.95g) in water (75ml) and ethanol (10ml) at 70°C was treated with 4,7-dichlorocinnoline (2.2g) and ethanol (10ml) was added. The resultant green suspension was stirred vigorously overnight at 70°C. The mixture was cooled, and the solid was filtered, washed with water and dried at room temperature to give 3.45g of the title compound as the monohydrate, melting point greater than 280°C.

Analysis:

Calculated for $C_{14}H_{10}ClN_3O_3S.H_2O$: C,47.53%; H, 3.42%; N, 11.88%

Found: C, 47.4%; H, 3.36; N, 11.71%.

The sulphonyl chloride hydrochloride derivative of the title compound is prepared from the title compound in a similar manner to that used in Example 1, last paragraph.

EXAMPLE 3

4-(7-Chloro-4-quinazolinylamino)-N-(2-diethylaminoethyl) benzenesulphonamide

4-(7-Chloro-4-quinazolinylamino)benzenesulphonyl chloride hydrochloride (36.0g obtainable from the title compound of Example 1) and methylene chloride (180ml) were cooled under nitrogen to 5°C. N,N-Diethylethylenediamine (35.4g) was then added at 5-10°C over 20 minutes to give a light yellow solution. The solution was stirred for 2 hours under nitrogen at 5° to 15°C and then water (200ml) was added. A white solid precipitated. The mixture was cooled to 10°C and the solid was filtered off, washed with water (2 x 40ml) and with chloroform (2 x 40ml) and dried in an oven to give 279g of title compound.

A 27g sample of the title compound was recrystallised and converted into the hydrochloride by the following procedure. The sample was dissolved in refluxing acetone (350ml). The mixture was filtered hot and solvent was distilled off to give a volume of 100ml of mixture. The mixture was cooled to about 10°C and then filtered. The white solid was collected, washed with acetone (2 x 50ml) and dried in an oven to give 23.5g of title compound.

The recrystallised title compound was suspended in isopropyl alcohol (100ml) and water (50ml). Concentrated hydrochloric acid was added until the pH of the mixture was 1. The mixture was stirred for 20 minutes and filtered and the collected solid was washed with water 2 x 15ml), isopropyl alcohol (2 x 30ml) and dried in an oven overnight to yield 185g of the title compound hydrochloride.

A sample of the title compound was converted into its hydrochloride by dissolving in warm ethanol and adding ethereal hydrogen chloride to give the title compound as its hydrochloride, three quarters ethanolate, m.p. 203°C.

Analysis:

Found: C, 51.5%; H, 5.86%; N, 13.5%

$C_{20}H_{24}ClN_5O_2S.HCl.\frac{3}{4}C_2H_6O$ requires C, 51.1%; H, 5.88%; N, 13.9%

EXAMPLE 4

1-[4-(7-Chloro-4-quinazolinylamino)benzenesulphonyl]-4-methylpiperazine

N-Methylpiperazine (1.0g, 0.01 mole) was dissolved in chloroform (50ml). Sodium carbonate (10g) was dissolved in water (50ml). The solutions were combined and cooled to 10°C. 4-(7-Chloro-4-quinazolinylamino)benzenesulphonyl chloride hydrochloride (3.85g, 0.01 mole) was added in portions to the

vigorously stirred solution. Stirring was continued for one hour. The chloroform layer was separated, dried and evaporated. The resulting gummy solid was redissolved in chloroform and chromatographed on an alumina column. Elution with chloroform gave a first band which was discarded. The second band was obtained as a low melting solid, which was converted to the hydrochloride by dissolving in ethanol and adding ethereal hydrogen chloride to give the title compound as the sesquihydrochloride (650mg) m.p. 237-239°C.

Analysis:
Found: C, 48.3%; H, 4.58%; N, 14.8%
$C_{19}H_{20}ClN_4O_2S.3/2HCl$ requires C, 48.7%; H, 4.80%; N, 14.7%

EXAMPLE 5

4-(7-Chloro-4-quinazolinylamino)-N-(1-ethyl-3-piperidyl)benzenesulphonamide

3-Amino-1-ethylpiperidine (1.1g, 0.0087 mole) was dissolved in chloroform (50ml), sodium carbonate (10g) was dissolved in water (50ml) and the combined solutions were cooled to 10°C. 4-(7-Chloro-4-quinazolinylamino) benzenesulphonyl chloride hydrochloride (3.4g, 0.0087 mole) was added in portions to the vigorously stirred solutions. Stirring was continued for one hour. The chloroform layer was separated, dried and evaporated to give a gummy solid which was triturated twice with benzene to give a colourless solid (1.1g). This was found to contain benzene. The solid was therefore chromatographed through an alumina column and eluted with chloroform to give a solid which was converted to the hydrochloride by dissolving in ethyl acetate and adding ethereal hydrogen chloride to give the title compound as its dihydrochloride (700mg). No definite m.p. was exhibited but the compound softens above 175°C.

The infra-red spectrum of the title compound exhibits prominent peaks at 2672, 1614, 1561, 1439, 1376, 1156, 1096, 880, 702 and 600 cm^{-1}.

Analysis:
Found: C, 48.2% H, 5.04%; N, 13.1%
$C_{21}H_{24}ClN_5O_2S.2HCl.¼H_2O$ requires C, 48.2%; 5.10%; N, 13.4%

EXAMPLE 6

4-[7-Chloro-4-cinnolinylamino]-N-(2-diethylaminoethyl) benzenesulphonamide

A mixture of anhydrous sodium carbonate (3.08g) and N,N-diethylethylenediamine (0.43ml) in chloroform (30ml) was vigorously stirred at 5°C and treated with 4-(7-Chloro-4-cinnolinylamino)benzenesulphonyl chloride hydrochloride (1.0g). The mixture was stirred at room temperature for 1½ hours and then filtered. The filtrate was evaporated to give a residue that crystallised from ethanol to give the title compound (0.456g), m.p. 175-76°C.

Analysis:
Found: C,55.3%; H, 5.6%; N, 16.0%
$C_{20}H_{24}ClN_5O_2S$ requires C, 55.36%; H, 5.57%; N, 16.14%

EXAMPLE 7

4-[7-Chloro-4-cinnolylamino]-N-(1-ethyl-3-piperidyl) benzenesulphonamide

3-Amino-1-ethylpiperidine (0.4ml) in chloroform (15ml) was treated with anhydrous sodium carbonate (2.94g) in water (15ml) and cooled to 3°C. The mixture was vigorously stirred and treated with 4-(7-chloro-4-cinnolinylamino)benzenesulphonylchloride hydrochloride (1.0g). The dark orange mixture was stirred at 3°C for 15 minutes, then at room temperature for 45 minutes. During this period the colour lightened considerably. The chloroform layer was separated and dried over magnesium sulphate. The residue on evaporation solidified when triturated with methanol, to give the title compound (0.5g), m.p. 213-15°C (with decomposition).

Analysis:
Found: C, 56.4; H, 5.6; N, 15.65%
$C_{21}H_{24}ClN_5O_2S$ requires C, 56.56; H, 5.42; N, 15.7%

EXAMPLE 8

4-(7-Chloro-4-quinazolinylamino)-N-[2-(1-pyrrolidinyl)ethyl]benzenesulphonamide

4-(7-Chloro-4-quinazolinylamino)benzene sulphonyl chloride, hydrochloride (3.5g, 0.011 mole) was added portionwise to a well-stirred mixture of sodium carbonate (11.5g) in water (120ml) and N-(2-aminoethyl)-pyrrolidine (1.26g, 0.01 mole) in chloroform (120ml) at about 10°C. After 1 hour at room temperature, the mixture was filtered. The chloroform layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give a gum. Trituration from ethyl acetate gave a white solid (1.4g) which could be crystallised from ethanol-water, m.p. 203-204.5°C.

Analysis:
Found: C, 56.0%; H, 5.40%; N, 16.1%
$C_{20}H_{22}ClN_5O_2S$ requires: C, 55.6%; H, 5.13%; N, 16.2%

EXAMPLE 9

4-(7-Chloro-4-quinazolinylamino)-N-[2-(1-ethyl)pyrrolidinyl) methyl]benzenesulphonamide

4-(7-Chloro-4-quinazolinylamino)benzenesulphonyl chloride hydrochloride (13.0g, 0.033 mole) was added portionwise to a well stirred mixture of sodium carbonate (33g) in water (350ml) and 2-(aminomethyl)-1-ethyl-pyrrolidine (4.3g, 0.033 mole) in chloroform (350ml), at 10°C. After 1 hour at room temperature, the mixture was filtered and the solid washed with water, then dried (vacuum oven). Recrystallisation from ethanol gave the title compound (6.74g), m.p. 199-201°C.

Analysis:

Found: C, 56.3%; H, 5.43%; N, 15.6%

$C_{21}H_{24}ClN_5O_2S$ requires: C, 56.6%; H, 5.42%; N, 15.7%

EXAMPLE 10

N-(3-Chloropropyl)-4-(7-chloro-4-quinazolinylamino)-Benzenesulphonamide

4-(7-Chloro-4-quinazolinylamino)benzenesulphonyl chloride hydrochloride (11.7g, 0.03 mole) was added portionwise to a well stirred mixture of sodium carbonate (45g) in water (350ml) and 3-chloropropylamine hydrochloride (3.9g, 0.03 mole) in chloroform (350ml) was added at 10°C. After about 1 hour at room temperature, the mixture was filtered and the solid was washed with water and then dried to give 7.4g of the title compound. A sample was recrystallised from a mixture of ethanol and water to give the title compound, m.p. 168-171°C.

Analysis:

Found: C, 50.0%; H, 4.07; N, 13.5%

$C_{17}H_{16}Cl_2N_4O_2S$ requires C, 49.6%; H, 3.92%; N, 13.6%

EXAMPLE 11

4-(7-Chloro-4-quinazolinylamino)-N-(3-diethylaminopropyl)benzenesulphonamide

A solution of the title compound of Example 10 (4.1g, 0.01 mole) in ethanol (120ml) containing diethylamine (20ml, 0.2 mole) was heated to 120° in a bomb for 5 hours and then left at room temperature overnight. Evaporation of the solvent under reduced pressure gave a crude red solid, which was chromatographed with alumina (basic) and 1% ethanol/chloroform. Recrystallisation from ethanol-water gave a white solid (1.43g). A second recrystallisation of a 1.0g sample from ethanol/water gave the title compound as the hemihydrate (0.84g), melting point 163-165°C.

Analysis:

Found: C, 54.9%; H, 5.61%; N, 15.3%

$C_{21}H_{26}ClN_5O_2S.\frac{1}{2}H_2O$ requires C, 55.2%; H, 5.96%; N, 15.3%

EXAMPLE 12

4-(7-Chloro-4-quinazolinylamino)-N-(2-diethylaminoethyl)benzenesulphonamide

(a) *N-(2-Chloroethyl)-4-(7-Chloro-4-quinazolinylamino)benzenesulphonamide*

This compound is prepared in a similar manner to Example 10 using 2-chloroethylamine hydrochloride (0.03 moles) instead of 3-chloropropylamine hydrochloride.

(b) *4-(7-Chloro-4-quinazolinylamino)-N-(2-diethylaminoethyl)benzenesulphonamide*

This compound can be prepared in a similar manner to Example 11 using the title compound of part (a) [0.01 mole] instead of the title compound of Example 10 and a bomb temperature of 100°C instead of 120°C.

EXAMPLE 13

4-(7-Chloro-4-cinnolinylamino)-N-(2-diethylaminoethyl)benzenesulphonamide

(a) *4-(7-Chloro-4-cinnolinylamino)-N-(2-chloroethyl)benzenesulphonamide*

This compound is prepared in a similar manner to the procedure of Example 10 using equimolar quantities of 2-chloroethylamine hydrochloride instead of 3-chloropropylamine hydrochloride and 4-(7-chloro-4-cinnolinylamino)benzenesulphonyl chloride hydrochloride instead of 4-(7-chloro-4-quinolinylamino) benzenesulphonyl chloride.

(b) *4-(7-Chloro-4-cinnolinylamino)-N-(2-diethylaminoethyl)benzenesulphonamide.*

This compound is prepared in a similar manner to Example 11 using the title compound of part (a) [0.01 mole] instead of the title compound of Example 10 and a bomb temperature of 100°C instead of 120°C.

EXAMPLE 14

(a) *4-(6-Chloro-4-quinazolinylamino)benzenesulphonic acid*

4,6-Dichloroquinazoline (5.9g, 0.03 mole) was added portionwise to sulphanilic acid (5.2g, 0.03 mole) in 50% aqueous ethanol (200ml) at 90°C with stirring. The mixture was refluxed for 2 hours, cooled and filtered. The solid was washed with 50% aqueous ethanol and dried in an oven to give the title compound (9.2g) as the hemihydrate m.p. greater than 300°C.

Analysis:

Found: C, 48.6%; H, 3.28%; N, 11.9%

$C_{14}H_{10}ClN_3O_3S$ requires C, 48.8%; H, 3.22%; N, 12.2%

(b) *4-(6-Chloro-4-quinazolinylamino)-N-(2-diethylaminoethyl)benzenesulphonamide*

The sulphonyl chloride hydrochloride derivative of the sulphonic acid of part (a) was used to sulphonylate N,N-diethylethylenediamine using a similar procedure to Example 8. The crude product obtained after evaporation of solvent from the chloroform layer was a brown solid which was purified by column chromatography (basic alumina: 1% ethanol/chloroform) to give a creamy white solid. Recrystallisation from ethanol/water gave the title compound hemihydrate, m.p. 110-113°C.

Analysis:

Calculated for $C_{20}H_{24}ClN_5O_2.\frac{1}{2}H_2O$ C, 54.2%; H, 5.69%; N, 15.8%

Found C, 54.3%; H, 5.64%; N, 16.1%

EXAMPLE 15

(a) *4-Acetylamino-N-[(1-ethyl-2-pyrrolidinyl)methyl]benzenesulphonamide*

4-Acetylaminobenzenesulphonyl chloride (7.3g, 0.03 mol) was added portionwise to a well stirred mixture of aqueous sodium carbonate (21.2g. in 250ml of water) and 2-aminomethyl-1-ethylpyrrolidine (4.0g. 0.03 mol) in chloroform (250ml) at about 10°. The ice bath used for cooling was removed. After 2 hours the chloroform layer was separated, dried ($MgSO_4$) and then evaporated under reduced pressure to give a gum, which slowly crystallised (11.6g). Recrystallisation from cold ethanol, followed by recrystallisation from water gave the pure title compound m.p. 94-96°C.

Analysis

Found: C, 52.5%; H, 7.39%; N, 12.0%

$C_{15}H_{23}N_3O_3S.H_2O$ requires C, 52.5%; H, 7.34%; N, 12.2%

(b) *4-Amino-N-[(1-ethyl-2-pyrrolidinyl)methyl]benzenesulphonamide*

4-Acetylamino-N-[(1-ethyl-2-pyrrolidinyl)methyl] benzenesulphonamide (6.5g, 0.02 mol) was dissolved in 50ml of 2N aqueous sodium hydroxide. The solution was heated to reflux, with stirring, for 1½ hours. The solution was cooled and the pH was adjusted to about 8 with hydrochloric acid (2N). The mixture was extracted with chloroform (3 x 50ml) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a solid (4.9). The solid was purified by column chromatorgaphy basis Al_2O_3: 1% ethanol/chloroform, followed by recrystallisation from water, to give the pure title compound m.p. 109-110°C.

Analysis:

Found: C, 55.2%; H, 7.59%; N, 15.1%

$C_{13}H_{21}N_3O_2S$ requires C, 55.1%; H, 7.47%; N, 14.8%

EXAMPLE 16

(a) *4-(7-Trifluoromethyl-4-quinazolinylamino)benzenesulphonic acid* 0.8 grams of sulphanilic acid and an equimolar quantity of 4-chloro-7-trifluoromethylquinazoline were heated in 20ml of 50% aqueous ethanol at 100°C for 2 hours. The suspension was cooled and the solid was filtered off, washed with water and dried to give 1.03g of the title compound. The sulphonyl chloride hydrochloride derivative for use in part (b) below was prepared in similar manner to Examples 1 and 2.

(b) *N-[(1-ethyl-2-pyrrolidinyl)methyl]-4-(7-trifluoromethyl-4-quinazolinylamino)benzamide*

A mixture of 2-aminomethyl-1-ethylpyrrolidine (0.34ml; 0.00235 mole), anhydrous sodium carbonate (3.5g) and chloroform (100ml) was cooled on an ice bath and treated with 4-(7-trifluoromethyl-4-quinazolinylamino)benzene sulphonylchloride hydrochloride (1.0g; 0.00235 mole) with vigorous stirring. The mixture was stirred at ambient temperature for 4 hours and then filtered. The residue on evaporation of the solvent was triturated with ether and the resulting solid was filtered off, washed with a little ether and dried to give the quarter hydrate of the title compound (0.28g), melting point 150-152°C.

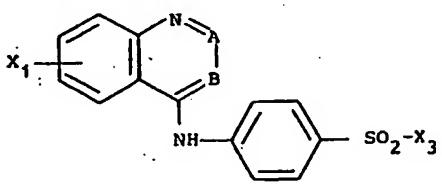
Analysis

Found: C, 54.4%; H, 5.0%; N, 14.8%;

$C_{22}H_{24}F_3N_5O_2S.\frac{1}{4}H_2O$ requires C, 54.59%; H, 5.1%; N, 14.47%.

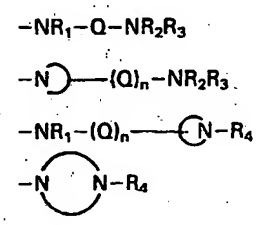
CLAIMS

1. A compound having the formula I



(I)

or a pharmaceutically acceptable salt thereof wherein one of A nd B is CH whilst the other one of A and B is N; X_1 is halogen or trifluoromethyl and X_3 represents a group having one of formulae II, III, IV and V



$-NR_1-Q-NR_2R_3$ (II)

$-N\bigcirc-(Q)_n-NR_2R_3$ (III)

$-NR_1-(Q)_n-\bigcirc N-R_4$ (IV)

$-N\quad N-R_4$ (V)

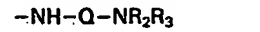
where Q is lower alkylene; R_1 is hydrogen or lower alkyl; R_2 and R_3 are, independently, lower alkyl or R_2 and R_3 together form a divalent radical such that R_2R_3NH is a secondary cyclic amine with 5 to 7 ring atoms; R_4 is lower alkyl; n is 0 or 1; the ring illustrated in formulae III and IV is a piperidine or pyrrolidine ring or a piperidine or pyrrolidine ring that is substituted on one or more ring carbon atoms by lower alkyl and the ring illustrated in formula V is a piperazine ring or a piperazine ring that is substituted on one or more ring carbon atoms by lower alkyl.

2. A compound as claimed in Claim 1 wherein X_1 is at the 7-position of the quinazoline or cinnoline ring system.

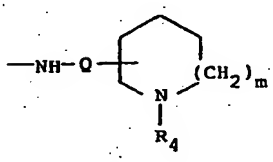
3. A compound as claimed in Claim 1 or Claim 2, wherein X_2 has formula II or IV wherein R_1 is hydrogen.

4. A compound as claimed in any one of Claims 1 to 3, wherein R_2 and R_3 are lower alkyl.

5. A compound as claimed in either one of Claims 1 and 2, wherein X_3 is a group having the formula IIa or IVa.



$-NH-Q-NR_2R_3$ (IIa)



(IVa)

wherein Q is alkylene of 1 to 4 carbon atoms; R_2, R_3 and R_4 are, independently, alkyl of 1 to 4 carbon atoms and m is 0 or 1.

6. 4-(7-Chloro-4-quinazolinylamino)-N-(2-diethylaminoethyl)benzenesulphonamide or a pharmaceutically acceptable salt thereof.

7. 4-(7-Chloro-4-cinnolinylamino)-N-(2-diethylaminoethyl)benzenesulphonamide or a pharmaceutically acceptable salt thereof.

8. 4-(6-Chloro-4-quinazolinylamino)-N-(2-diethylaminoethyl)benzenesulphonamide or a pharmaceutically acceptable salt thereof.

9. 4-[7-Chloro-4-quinazolinylamino]-N-(1-ethyl-3-piperidyl)benzenesulphonamide or a pharmaceutically acceptable salt thereof.

10. 4-[7-Chloro-4-cinnolinylamino)-N-(1-ethyl-3-piperidyl)benzenesulphonamide or a pharmaceutically acceptable salt thereof.

11. 1-[4-(7-Chloro-4-quinazolinylamino)benzenesulphonyl]-4-methylpiperazine or a pharmaceutically acceptable salt thereof.

12. 4-(7-Chloro-4-quinazolinylamino)-N-[2-(1-pyrrolidinyl)ethyl]benzenesulphonamide or a pharmaceutically acceptable salt thereof.

13. 4-(7-Chloro-4-quinazolinylamino)-N-[(2-(1-ethyl)pyrrolidinyl)methyl]benzenesulphonamide or a pharmaceutically acceptable salt thereof.

14. 4-(7-Chloro-4-quinazolinylamino)-N-(3-diethylaminopropyl)benzenesulphonamide or a pharmaceutically acceptable salt thereof.

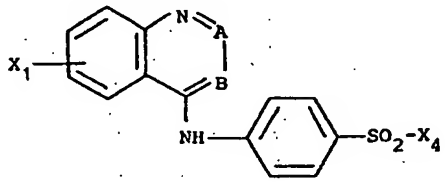
15. N-[2-diethylaminoethyl]-4-[7-trifluoromethyl-4-quinazolinylamino]benzenesulphonamide or a pharmaceutically acceptable salt thereof.

16. A compound as claimed in any one of Claims 1 to 15 for use as a pharmaceutical.

17. Use of a compound as claimed in any one of Claims 1 to 15 to prepare a medicament for anti-hypertensive use.

18. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 15 in association or combination with a pharmaceutically acceptable carrier.

19. A compound having the formula



(VI)

or a salt thereof, wherein X_1 is halogen or trifluoromethyl; one of A and B is CH whilst the other one of A and B is N; and X_4 represents $-OH$ or $-NR_1R_5$ where R_1 is hydrogen or lower alkyl and R_5 is hydrogen or a group having the formula $-Q-Z$ where Q is lower alkylene and Z is a leaving group or atom.

20. A compound as claimed in Claim 19 wherein X_1 is at the 7-position of the quinazoline or cinnoline ring.

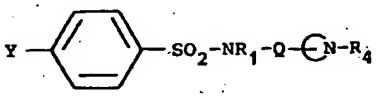
21. 4-[7-Chloro-4-quinazolinylamino]benzenesulphonic acid or a salt thereof.

22. 4-[7-Chloro-4-cinnolinylamino]benzenesulphonic acid or a salt thereof.

23. 4-[6-Chloro-4-quinazolinylamino]benzenesulphonic acid or a salt thereof.

24. 4-[7-Trifluoromethyl-4-quinazolinylamino]-benzenesulphonic acid or a salt thereof.

25. A compound having the formula



(IVb)

where Y is amino, protected amino or latent amino, R_1 is hydrogen or lower alkyl, R_4 is lower alkyl and the ring attached to Q and R_4 is a piperidine or pyrrolidine ring or a piperidine or pyrrolidine ring substituted on one or more ring carbon atoms by lower alkyl.

26. 4-Amino-N-[(2-(1-ethyl)pyrrolidinyl)methyl]-benzenesulphonamide or a salt thereof.

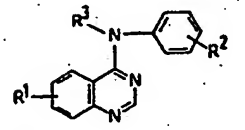
Printed in the UK for HMSO, D8818935, 1085, 7102.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

(12) UK Patent Application (19) GB (11) 2 033 894 A

(21) Application No 7931441
(22) Date of filing 11 Sep 1979
(30) Priority data
(31) 53/111484
(32) 11 Sep 1978
(33) Japan (JP)
(43) Application published
29 May 1980
(51) INT CL³
C07D 239/94
A61K 31/505
(52) Domestic classification
C2C 1604 213 220 22Y 250
252 25Y 29X 29Y 30Y 311
313 314 31Y 322 323 32Y
332 337 338 364 36Y 456
45Y 610 611 617 618 620
621 624 660 662 670 671
680 694 698 69Y 775 802
80Y AA LH NF
(56) Documents cited
Chemical Abstracts Vol
85 63018
Chemical Abstracts Vol
79 13783e
(Indian J. Chem. 11 (6)
538-40)
Chemical Abstracts Vol.
76 153706d
Chemical Abstracts Vol
76 34199f
(58) Field of search
C2C
(71) Applicants
Sankyo Company,
Limited,
1-6, 3-chome,
Nihonbashi Honcho,
Chuo-ku,
Tokyo,
Japan.
(72) Inventors
Shinsaku Kobayashi,
Katsuo Kamoshita,
Shigeki Nagai,
Takeo Honda,
Kiroku Oda,
Katsutoshi Fujii,
Takashi Kobayashi,
Mikio Kojima.
(74) Agents
Marks & Clerk

(54) **4-Anilinoquinazolines**

(57) Novel compounds of the formula (I):



(I)

(in which:
R^1 represents a hydrogen atom, a halogen atom, a trifluoromethyl group or a nitro group;
R^2 represents a hydrogen atom, an alkyl group, an alkoxy group or a halogen atom; and
R^3 represents a hydrogen atom or an alkyl group)
and pharmaceutically acceptable salts thereof are, except where R^1 represents a hydrogen atom or a chlorine atom in the 6- position when R^2 and R^3 both represent hydrogen atoms, which have been found to possess valuable analgesic and anti-inflammatory activities, can be prepared by heating the appropriate 4-haloquinazoline with an appropriate aniline derivative.

GB 2 033 894 A

SPECIFICATION

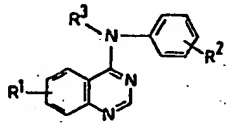
New 4-anilinoquinazoline derivatives and their preparation

The present invention relates to a series of new 4-anilinoquinazoline derivatives, to a process for their preparation and to their use as analgesic and anti-inflammatory agents.

A wide range of analgesic and anti-inflammatory agents is available, suitable for treating pain of all intensity from mild (treated with aspirin, paracetamol or the like) to intense (treated with a narcotic analgesic, such as morphine or pentazocine). However, all of these known compounds have side effects, which may range from stomach irritation in the case of aspirin to dizziness, drowsiness and nausea and, in the case of the narcotic analgesics, may include dependence The incidence and severity of these side effects varies from person to person and there is, therefore, a continuing need for new classes of anagesic for administration to persons to whom administration of existing analgesics would be inappropriate.

We have now surprisingly discovered that a class of 4-anilinoquinazoline derivatives possesses analgesic and anti-inflammatory activity comparable with, but in many cases substantially better than, that of aspirin. Although aminoquinazolines, including 4-anilinoquinazoline and 4-anilino-6-chloroquinazoline, are known [see, for example, J. Org. Chem., *41*, 2646 (1976) and U. S. Patent Specification No. 3,985,749], they have hitherto been proposed for use in the treatment of coccidiosis and we are not aware of any prior suggestions that they have analgesic or anti-inflammatory activity.

The 4-anilinoquinazoline derivatives which may be prepared by the process of the invention are those compounds of formula (I):



(I)

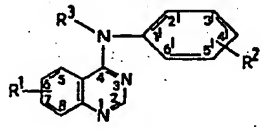
in which:

R^1 represents a hydrogen atom, a halogen atom, a trifluoromethyl group or a nitro group;

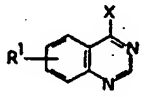
R^2 represents a hydrogen atom, an alkyl group, an alkoxy group or a halogen atom; and

R^3 represents a hydrogen atom or an alkyl group; and pharmacologically acceptable acid addition salts thereof.

Of these compounds, all are *per se* new, except those compounds in which R^1 represents a hydrogen atom or a chlorine atom in the 6- position and R^2 and R^3 both represent hydrogen atoms. Throughout this Specification, the numbering adopted for the ring systems in the anilinoquinazoline derivatives of the invention is as shown below

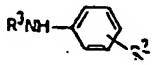


The process of the invention comprises heating a haloquinazoline derivative of formula (II):



(II)

(in which R^1 is as defined above and X represents a halogen atom) with aniline or an aniline derivative of formula (III):



(III)

(in which R^2 and R^3 are as defined above).

The invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, one or more of the new 4-anilinoquinazoline derivatives of the present invention.

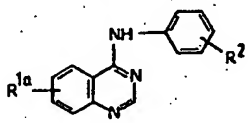
In the above formulae, R^1 represents a hydrogen atom, a halogen atom, a trifluoromethyl group or a nitro group and, where R^1 represents a halogen atom, it is preferably a fluorine, chlorine or bromine atom.

Where R^2 represents an alkyl group, this is preferably a lower alkyl group and most preferably a straight or branched chain alkyl group having from 1 to 4 carbon atoms, e.g. a methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl group. Where R^2 represents an alkoxy group, this is preferably a lower alkoxy group and most

preferably a straight or branched chain alkoxy group having from 1 to 4 carbon atoms, e.g. a methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy or isobutoxy group. Where R^2 represents a halogen atom, this is preferably a fluorine, chlorine or bromine atom.

Where R^3 represents an alkyl group, this is preferably a lower alkyl group and more preferably a straight or branched chain alkyl group having from 1 to 4 carbon atoms e.g. a methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl group.

Among the compounds of the invention where R^3 represents a hydrogen atom, a preferred class are those compounds of formula (Ia):



(Ia)

(in which R^{1a} represents a halogen atom or a trifluoromethyl group and R^2 is as defined above, provided that R^{1a} does not represent a chlorine atom at the 6- position when R^2 represents a hydrogen atom) and pharmacologically acceptable acid addition salts thereof.

More preferred compounds within this class are those in which R^{1a} represents a halogen atom at the 7- position or a trifluoromethyl group at the 7- or 8- position and R^2 is as defined above and most preferred compounds are those in which R^{1a} represents a chlorine atom at the 7- position or a trifluoromethyl group at the 7- or 8- position and R^2 represents a hydrogen atom, a methyl group, a methoxy group or a chlorine atom.

Among the compounds in which R^3 represents an alkyl group, particularly preferred compounds are those in which:

R^1 represents a hydrogen atom, or a chlorine atom, a trifluoromethyl group or a nitro group at the 7- or 8- position;

R^2 represents a hydrogen atom, or a methyl group, ethyl group, methoxy group, ethoxy group or chlorine atom at the 4'- position; and

R^3 represents a methyl group or an ethyl group.

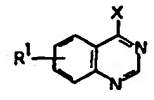
Examples of compounds in accordance with the present invention are listed below. The numbers appended to the compounds in the following list are used to identify them subsequently in the Specification.

1. 4-Anilino-5-chloroquinazoline.
2. 4-Anilino-5-chloroquinazoline hydrochloride.
3. 6-Chloro-4-(3-methylanilino)quinazoline.
4. 6-Chloro-4-(3-methylanilino)quinazoline hydrochloride.
5. 4-Anilino-7-chloroquinazoline.
6. 4-Anilino-7-chloroquinazoline hydrochloride.
7. 7-chloro-4-(4-methylanilino)quinazoline.
8. 7-Chloro-4-(4-methylanilino)quinazoline hydrochloride.
9. 7-CHLORO-½-(4-methoxyanilino)quinazoline.
10. 7-Chloro-4-(4-methoxyanilino)quinazoline hydrochloride.
11. 7-Chloro-4-(2-chloroanilino)quinazoline.
12. 7-Chloro-4-(2-chloroanilino)quinazoline hydrochloride.
13. 4-Anilino-8-chloroquinazoline.
14. 4-Anilino-8-chloroquinazoline hydrochloride.
15. 4-Anilino-7-fluoroquinazoline.
16. 4-Anilino-7-fluoroquinazoline hydrochloride.
17. 4-Anilino-7-trifluoromethylquinazoline.
18. 4-Anilino-7-trifluoromethylquinazoline hydrochloride.
19. 4-Anilino-8-trifluoromethylquinazoline.
20. 4-Anilino-8-trifluoromethylquinazoline hydrochloride.
21. 6-Chloro-4-(4-chloroanilino)quinazoline.
22. 6-Chloro-4-(4-chloroanilino)quinazoline hydrochloride.
23. 6-Chloro-4-(4-methylanilino)quinazoline.
24. 6-Chloro-4-(4-methylanilino)quinazoline hydrochloride.
25. 5-Chloro-4-(3-chloroanilino)quinazoline.
26. 5-Chloro-4-(3-chloroanilino)quinazoline hydrochloride.
27. 6-Chloro-4-(2-chloroanilino)quinazoline.
28. 6-Chloro-4-(2-chloroanilino)quinazoline hydrochloride.
29. 4-(4-Bromoanilino)-6-chloroquinazoline.
30. 4-(4-Bromoanilino)-6-chloroquinazoline hydrochloride.
31. 6-Chloro-4-(2-methoxyanilino)quinazoline.
32. 6-Chloro-4-(2-methoxyanilino)quinazoline hydrochloride.
33. 7-Chloro-4-(4-chloroanilino)quinazoline.
34. 7-Chloro-4-(4-chloroanilino)quinazoline hydrochloride.

35. 7-Chloro-4-(2-methylanilino)quinazoline.
36. 7-Chloro-4-(2-methylanilino)quinazoline hydrochloride.
37. 6-Chloro-4-(2-methylanilino)quinazoline.
38. 6-Chloro-4-(2-methylanilino)quinazoline hydrochloride.
39. 7-Chloro-4-(3-chloroanilino)quinazoline.
40. 7-Chloro-4-(3-chloroanilino)quinazoline hydrochloride.
41. 7-Chloro-4-(3-methylanilino)quinazoline.
42. 7-Chloro-4-(3-methylanilino)quinazoline hydrochloride.
43. 7-Chloro-4-(4-ethylanilino)quinazoline.
44. 7-Chloro-4-(4-ethylanilino)quinazoline hydrochloride.
45. 4-(4-Butylanilino)-7-chloroquinazoline.
46. 4-(4-Butylanilino)-7-chloroquinazoline hydrochloride.
47. 7-Chloro-4-(4-ethoxyanilino)quinazoline.
48. 7-Chloro-4-(4-ethoxyanilino)quinazoline hydrochloride.
49. 8-Chloro-4-(3-chloroanilino)quinazoline.
50. 8-Chloro-4-(3-chloroanilino)quinazoline hydrochloride.
51. 4-(4-Methoxyanilino)-7-trifluoromethyl-quinazoline.
52. 4-(4-Methoxyanilino)-7-trifluoromethyl-quinazoline hydrochloride.
53. 4-(*N*-Methylanilino)quinazoline.
54. 4-(*N*-Methylanilino)quinazoline hydrochloride.
55. 7-Chloro-4-(*N*-methylanilino)quinazoline.
56. 7-Chloro-4-(*N*-methylanilino)quinazoline hydrochloride.
57. 7-Chloro-4-(*N*-ethylanilino)quinazoline.
58. 7-Chloro-4-(*N*-ethylanilino)quinazoline hydrochloride.
59. 7-Chloro-4-(4,*N*-dimethylanilino)quinazoline.
60. 7-Chloro-4-(4,*N*-dimethylanilino)quinazoline hydrochloride.
61. 7-Chloro-4-(4-ethyl-*N*-methylanilino)-quinazoline.
62. 7-Chloro-4-(4-ethyl-*N*-methylanilino)-quinazoline hydrochloride.
63. 7-Chloro-4-(4-methoxy-*N*-methylanilino)-quinazoline.
64. 7-Chloro-4-(4-methoxy-*N*-methylanilino)-quinazoline hydrochloride.
65. 7-Chloro-4-(4-ethoxy-*N*-methylanilino)-quinazoline.
66. 7-Chloro-4-(4-ethoxy-*N*-methylanilino)-quinazoline hydrochloride.
67. 7-Chloro-4-(4-chloro-*N*-methylanilino)-quinazoline.
68. 7-Chloro-4-(4-chloro-*N*-methylanilino)-quinazoline hydrochloride.
69. 7-Chloro-4-(4-chloro-*N*-ethylanilino)-quinazoline.
70. 7-Chloro-4-(4-chloro-*N*-ethylanilino)-quinazoline hydrochloride.
71. 8-Chloro-4-(*N*-methylanilino)quinazoline.
72. 8-Chloro-4-(*N*-methylanilino)quinazoline hydrochloride.
73. 4-(*N*-Methylanilino)-7-trifluoromethyl-quinazoline.
74. 4-(*N*-Methylanilino)-7-trifluoromethyl-quinazoline hydrochloride.
75. 4-(4-Methoxy-*N*-methylanilino)-7-trifluoromethylquinazoline.
76. 4-(4-Methoxy-*N*-methylanilino)-7-trifluoromethylquinazoline hydrochloride.
77. 4-(*N*-Methylanilino)-8-trifluoromethylquinazoline.
78. 4-(*N*-Methylanilino)-8-trifluoromethyl-quinazoline hydrochloride.
79. 4-(*N*-Methylanilino)-7-nitroquinazoline.
80. 4-(*N*-Methylanilino)-7-nitroquinazoline hydrochloride.

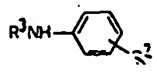
Of these compounds, particularly valuable compounds have been found to be Compounds Nos. 5, 17, 55 and 73, as well as their acid addition salts, particularly the hydrochlorides (that is to say, Compounds Nos. 6, 18, 56 and 74); of these, the most preferred compound is Compound No. 5 and its acid addition salts, particularly the hydrochloride, Compound No. 6.

The compounds of formula (I) can be prepared by heating a corresponding haloquinazoline derivative of formula (II):



(II)

with aniline or an aniline derivative of formula (III):



(III)

(in which R^1, R^2, R^3 and X are as defined above). X is preferably a chlorine, bromine or iodine atom.

The process of the invention is preferably carried out in the presence of a solvent, although the nature of the solvent is not critical, provided that it has no adverse effect upon the reaction. Preferred solvents are:

alcohols, such as methanol or ethanol; ethers, such as tetrahydrofuran or dioxan; aromatic hydrocarbons, such as benzene or toluene; or halogenated aromatic hydrocarbons, such as 2,4-dichlorobenzene. The precise ratio of haloquinazoline derivative (II) to aniline or aniline derivative (III) is also not critical; however, for reasons of economy, we prefer to employ approximately equimolar amounts of the two reagents. Since the reaction is exothermic, the reaction temperature, too, is not critical. The reaction is most conveniently carried out by heating the reaction mixture to approximately the boiling temperature of the solvent employed. The reaction can be accelerated by the use of a catalytic amount of a mineral acid, such as hydrochloric acid or sulphuric acid.

The reagents can be mixed in any order; for example, the haloquinazoline derivative (II) can be mixed with the appropriate amount of the aniline or aniline derivative (III), after which the solvent is added and the mixture is heated; alternatively, the aniline or aniline derivative (III) is added to a solution containing appropriate amount of the haloquinazoline derivative (II) and the resulting solution is heated. The time required for the reaction will depend upon the nature of the reagents, the reaction temperature and other conditions; however, the reaction will normally take from 5 minutes to 5 hours.

When the reaction is carried out under the conditions described above, the compound of formula (I) is normally obtained in the form of its salt with the hydrohalic acid HX, although the compound (I) is occasionally obtained in the form of the free base, in which case a portion of the aniline derivative (III) has acted as an acid binding agent, and this can be favoured if the amount of aniline derivative (III) employed is greater than equimolar. However, a better way of ensuring that the compound (I) is obtained in the form of a free base is to carry out the reaction in the presence of a base (e.g. triethylamine) as acid binding agent. In this case, the preferred procedure is to dissolve the haloquinazoline derivative (II) in a water-immiscible organic solvent (such as benzene, toluene or 2,4-dichlorobenzene), to add to the resulting solution the desired amount (preferably an equimolar amount) of the aniline or aniline derivative (III) and 1.2 times an equimolar amount of an acid binding agent, and then to heat the reaction mixture to about the boiling temperature of the solvent employed for a period of from 3 to 5 hours.

When the reaction is complete, the desired compound may be recovered from the reaction mixture by conventional means. For example, one suitable recovery sequence comprises: if necessary, distilling off the solvent from the reaction mixture; optionally adding the residue to water or to an inert organic solvent and then separating the compound by filtration; and finally recrystallizing the compound from a suitable organic solvent. Where the desired compound is obtained in the form of a free base by carrying out the reaction in the presence of an acid binding agent and a water-immiscible organic solvent, a preferred recovery sequence comprises: adding water to the reaction mixture; separating and then drying the organic phase; distilling the solvent from this organic phase under reduced pressure; and finally recrystallizing the desired compound from a suitable organic solvent.

Where the compound has been produced in the form of an hydrohalide salt and it is desired to obtain the free base, the salt is treated with a dilute aqueous solution of an alkali (such as sodium hydroxide or potassium hydroxide) and the precipitated product is collected by filtration, washed with water and recrystallized from a suitable organic solvent; this may be carried out either before or after separation of the hydrohalide salt from the initial reaction mixture.

Where the free base form of the compound of formula (I) has been obtained, this may, if desired, be converted to a pharmacologically acceptable acid addition salt by conventional salification techniques. Suitable salts include acid addition salts of mineral acids (such as hydrochloric acid, hydrobromic acid or hydroiodic acid) or acid addition salts of organic acids (such as oxalic acid, maleic acid, fumaric acid, tartaric acid or citric acid).

Surprisingly, the anilinoquinazoline derivatives of the present invention have excellent analgesic and anti-inflammatory activities, as demonstrated by the following tests.

Test for analgesic activity

This test employs a bradykinin-induced nociceptive stimulus and is a partially modified version of the test described by Deffenu [J. Pharm. Pharmac. *18*, 135 (1966)] and Blane [J. Pharm. Pharmac., *19*, 367 (1967)]. The test animals were female Hartley guinea pigs having a body weight of from 350 g to 400 g. The guinea pigs were divided into groups, each group containing from 5 to 10 animals. The test animals were cannulated retrogradely into the carotid artery under the anesthesia induced by intraperitoneal injection of 20 mg/kg of pentobarbital. The guinea pigs were allowed to recover from the anesthesia for at least 3 hours before the tests commenced.

The test compounds listed in the following Table 1 were administered orally. Immediately before administration of each test compound and then 15, 30, 60, 90 and 120 minutes after administration, each guinea pig was administered with 0.5 ug of bradykinin through the cannula. Turning of the head or twisting of the front legs upon injection was taken as a sign of nociceptive response. The test compounds were administered at various doses and the inhibition rate was determined accordingly.

Test for anti-inflammatory activity

Male Wistar-Imamichi rats, each weighing approximately 150 g, were used in these experiments and were divided into groups, each containing 5 animals. Each of the test compounds listed in Table 2 was administered orally, at various doses, to the rats and then, 30 minutes after oral administration, 0.05 ml of a

1% w/v carrageenin suspension was subcutaneously injected into the sole of the right hind paw to induce oedema. The volume of the paw was measured both before and 3 hours after injection of the carrageenin by the method of Winder et al [Arch. Int. Pharmacodyn. *112*, 174 (1957)]. The difference between the volume of the paw before and after injection was defined as the oedema intensity. The inhibition rate was the ratio of the oedema intensity in groups to which the test compounds had been administered to control groups, to which no test compounds had been administered.

For both of the above tests, the ID_{50} was calculated by the method of Litchfield and Wilcoxon [J. Pharmacol. Exptl. Therap. *96*, 99 (1949)] on the basis of the inhibition rates obtained as described above. The results are shown in Table 1, in which the compounds of the invention are identified by the numbers heretofore assigned to them.

TABLE 1

Test Compound	ID_{50} (mg/kg) per os	
	Analgesic Activity	Anti-inflammatory Activity
5	25	28
17	16.5	20
55	50	36
73	31	15.5
Controls		
Mefenamic acid	72	50
Aspirin	280	145

It is apparent from the results shown above that the compounds of the invention have valuable analgesic and anti-inflammatory activities comparable with or better than those of aspirin and mefenamic acid.

The compounds of the invention can be administered orally in the form of tablets, capsules, granules, powders or syrups or through the intestines in the form of a suppository. The dosage depends on the symptoms, age and body weight of the patient, but is usually from 50 mg to 2000 mg per day for an adult, in a single dose or in divided doses.

The preparation of the compounds of the invention is further illustrated by the following non-limiting Examples.

EXAMPLE 1

4-Anilino-5-chloroquinazoline hydrochloride (Compound No. 2)

A solution of 3.0 g of 4,5-dichloroquinazoline and 1.4 g of aniline in 20 ml of ethanol was heated, whereupon a violent reaction occurred and the reaction mixture solidified. After cooling, the solidified product was collected and recrystallized from ethanol to give 1.8 g (yield 46%) of the desired Compound No. 2 in the form of a pale yellow powder melting at 263-267°C (with decomposition).

Elemental Analysis:

Calculated for $C_{14}H_{11}N_3Cl_2$:
C, 57.55%; H, 3.80%; N, 14.38%.
Found: C, 57.70%; H, 4.15%; N, 14.25%.

EXAMPLE 2

6-Chloro-4-(3-methylanilino)quinazoline hydrochloride (Compound No. 4)

4.0 g of 4,6-dichloroquinazoline were dissolved in 50 ml of dioxan and then 2.0 g of *m*-toluidine were added. The mixture was then heated to reflux for 3 hours at 100°C. After completion of the reaction, the precipitated product was collected by filtration and recrystallized from ethanol to afford 3.7 g (yield 60%) of the desired Compound No. 4, in the form of pale yellow needles melting at 251 - 254°C (with decomposition).

Elemental Analysis:
Calculated for $C_{15}H_{13}N_3Cl_2$:
C, 59.01%; H, 4.26%; N, 13.77%.
Found: C, 58.70%; H, 4.20%; N, 13.40%.

EXAMPLES 3 - 5

Following the procedures described in Examples 1 and 2, the hydrochlorides listed and identified in Table 2 were obtained.

TABLE 2

Ex. No.	Cpd. No.	Melting point	Appearance	Yield
3	6	271 - 273°C (decomposition)	pale yellow needles	38%
4	22	276 - 280°C (decomposition)	pale yellow needles	46%
5	24	264 - 265°C (decomposition)	yellow powder	62%

EXAMPLE 6

4-Anilino-7-chloroquinazoline (Compound No. 5)

8.0 g of 4,7-dichloroquinazoline were dissolved in 250 ml of benzene, and then 4.0 g of aniline and 4.8 g of triethylamine were added to the solution. The resulting mixture was heated to reflux for 5 hours, with stirring. After completion of the reaction, 200 ml of water were added to the reaction mixture. The mixture was shaken and the benzene phase was separated and dried over anhydrous sodium sulphate. The benzene was distilled off and the resulting crystals were recrystallized from ethyl acetate to give 8.5 g (yield 83%) of the desired Compound No. 5 in the form of colourless granules having a melting point of 215 - 217°C.

Elemental Analysis:
Calculated for $C_{14}H_{10}N_3Cl$:
C, 65.76%; H, 3.94%; N, 16.43%.

Found: C, 65.81%; H, 3.61%; N, 16.29%.

EXAMPLES 7 - 12

Following the procedure described in Example 6, there were obtained the compounds listed in Table 3, in which the compounds obtained are identified by the numbers heretofore assigned to them.

TABLE 3

Ex. No.	Cpd. No.	Melting Point	Appearance	Yield
7	25	133 - 135°C	colourless powder	41%
8	27	245 - 251°C	yellow granules	38%
9	29	218 - 220°C	pale yellow needles	24%
10	31	137 - 139°C	colourless needles	59%
11	33	206 - 208°C	colourless powder	35%
12	35	155 - 158°C	colourless needles	52%

EXAMPLE 13

4-Anilino-8-chloroquinazoline
(Compound 13)

15 ml of ethanol were added to a mixture of 3.0 g of 4,8-dichloroquinazoline and 1.9 g of aniline, and then the mixture was heated. The reagents dissolved and immediately solidified. After cooling, the solidified product was collected, washed with ethanol and then recrystallized from ethanol to give 1.9 g (yield 48%) of the desired Compound No. 13 in the form of colourless crystals having a melting point of 206°C (with decomposition).

Elemental Analysis:

Calculated for $C_{14}H_{10}N_3Cl.0.5H_2O$:
C, 63.52%; H, 4.19%; N, 15.87%.

Found: C, 63.50%; H, 4.30%; N, 15.45%.

EXAMPLES 14 - 22

Following the procedure described in Example 13, the hydrochlorides listed in Table 4 were obtained; these compounds are identified by the numbers heretofore assigned to them.

TABLE 4

Ex. No.	Cpd. No.	Melting point	Appearance	Yield
14	8	>280°C	yellow powder	33%
15	12	237 - 241°C (decomposition)	pale yellow powder	43%
16	38	200 - 203°C	pale yellow powder	52%
17	40	286 - 290°C (decomposition)	pale yellow powder	33%
18	42	248 - 251°C (decomposition)	yellow powder	38%
19	44	>280°C	yellow granules	40%
20	46	247 - 250°C (decomposition)	yellow powder	53%
21	48	265 - 268°C (decomposition)	pale yellow needles	55%
22	50	224°C (decomposition)	pale yellow powder	55%

EXAMPLE 23

4-Anilino-7-trifluoromethylquinazoline
(Compound No. 17)

2.5 g of 4-chloro-7-trifluoromethylquinazoline were dissolved in 10 ml of ethanol, and 1.0 g of aniline was added to the solution. Reaction occurred violently and the reaction mixture solidified immediately. After cooling, the solidified product was collected and washed with ethanol. The resulting crystals were pulverized and added to a dilute aqueous solution of sodium hydroxide. Insolubles were filtered off and recrystallized from ethanol to give 1.7 g (yield 60%) of the desired Compound No. 17 in the form of colourless plates melting at 230 - 232°C.

Elemental Analysis:
Calculated for $C_{15}H_{10}N_3F_3$:
C, 62.28%; H, 3.48%; N, 14.53%.

Found: C, 62.50%; H, 3.50%; N, 14.50%.

EXAMPLE 24
7-Chloro-4-(4-methoxyanilino)quinazoline
(Compound No. 9)

5 ml of ethanol were added to a mixture of 4.8 g of 4,7-dichloroquinazoline and 3.0 g of *p*-anisidine. The resulting mixture was heated, whereupon the solids dissolved and then the mixture immediately solidified. After cooling, the solidified compound was collected and washed with, in turn, ethanol, dilute aqueous sodium hydroxide and water. The resulting crystals were re-crystallized from ethanol to give 4.0 g (yield 51%) of the desired Compound No. 9 in the form of pale yellow plates melting at 177 - 179°C.

Elemental Analysis:
Calculated for $C_{15}H_{12}ON_3Cl.C_2H_5OH$:
C, 61.54%; H, 5.47%; N, 12.66%.

Found: C, 61.30%; H, 5.50%; N, 12.50%.

EXAMPLE 25
7-Chloro-4-(4-methoxyanilino)quinazoline hydrochloride
(Compound No. 10)

5 ml of ethanol were added to a mixture of 4.8 g of 4,7-dichloroquinazoline and 3.0 g of *p*-anisidine. The resulting mixture was heated, whereupon the solids dissolved and the reaction mixture immediately then solidified. After cooling, the solidified product was collected and washed with ethanol and the resulting crystals were recrystallized from ethanol, giving 2.0 g (YIELD ¾¼⅔(OF THE DESIRED Compound No. 10 in the form of a fine pale yellow powder having a melting point of 276 - 279°C (with decomposition).

Elemental Analysis:
Calculated for $C_{15}H_{13}ON_3Cl_2$:
C, 55.91%; H, 4.07%; N, 13.04%.

Found: C, 55.50%; H, 4.00%; N, 12.80%.

EXAMPLE 26
4-(4-Methoxyanilino)-7-trifluoromethylquinazoline
(Compound No. 51)

5 ml of ethanol were added to a mixture of 2.3 g of 4-chloro-7-trifluoromethylquinazoline and 1.4 g of *p*-anisidine. The resulting mixture was heated to dissolve the solids, whereupon the solution solidified immediately. After cooling, the resulting crystals were collected by filtration and washed with, in turn, ethanol, dilute aqueous sodium hydroxide and water. The resulting crystals were recrystallized from ethanol, to give 2.5 g (yield 78%) of the desired Compound No. 51 in the form of colourless needles melting at 190 - 194°C.

Elemental Analysis:
Calculated for $C_{16}H_{12}ON_3F_3$:
C, 60.18%; H,3.76%; N, 13.16%.

Found: C, 59.80%; H, 3.80%; N, 12.80%.

EXAMPLE 27
7-Chloro-4-(N-methylanilino)quinazoline hydrochloride
(Compound No. 56)

A solution of 3.0 g of 4,7-dichloroquinazoline and 1.7 g of *N*-methylaniline in 10 ml of ethanol was heated for 10 minutes. After completion of the reaction, the ethanol was distilled off and the resulting crystals were recrystallized from a small amount of ethanol to give 2.4 g (yield 46%) of the desired Compound No. 56 in the form of pale yellow granules melting at 230 - 233°C (with decomposition).

Elemental analysis:
Calculated for $C_{15}H_{13}N_3Cl_2$:
C, 59.01%; H, 4.26%; N, 13.77%.

Found: C, 58.95%; H, 4.20%; N, 13.80%.

EXAMPLE 28

7-Chloro-4-(N-ethylanilino)quinazoline hydrochloride (Compound No. 58)

A mixture of 3.0 g of 4,7-dichloroquinazoline and 2.0 g of *N*-ethylaniline in 10 ml of ethanol was heated for 5 minutes. After completion of the reaction the reaction mixture was cooled, whereupon crystals separated. These were collected by filtration and recrystallized from a small amount of ethanol to give 2.0 g (yield 47%) of the desired Compound No. 58 in the form of pale yellow needles melting at 222 - 226°C (with decomposition).

Elemental Analysis:

Calculated for $C_{16}H_{15}N_3Cl_2$:
C, 60.18%; H, 4.70%; N, 13.16%.

Found: C, 60.00%; H, 4.85%; N, 13.10%.

EXAMPLES 29 and 30

Following the procedures described in Examples 27 and 28, the hydrochlorides shown in Table 5 were obtained.

TABLE 5

Ex. No.	Cpd. No.	Melting Point	Appearance	Yield
29	54	243 - 245°C (decomposition)	pale yellow needles	80%
30	72	179 - 182°C (decomposition)	pale yellow needles	53%

EXAMPLE 31

4-(N-Methylanilino)-7-trifluoromethylquinazoline (Compound No. 73)

2.5 g of 4-chloro-7-trifluoromethylquinazoline and 1.2 g of *N*-methylaniline were added, in turn, to 5 ml of ethanol, and then the mixture was heated until it became a homogeneous solution. At the end of this time, the ethanol was distilled off and the residual crystals were recrystallized from a 9 : 1 by volume mixture of ethanol and water, to give 1.4 g (yield 46%) of the desired Compound No. 73 in the form of colourless granules melting at 135 - 137°C.

Elemental Analysis:

Calculated for $C_{16}H_{12}N_3F_3$:
C, 63.36%; H, 3.96%; N, 13.86%.

Found: C, 63.25%; H, 4.00%; N, 14.05%.

EXAMPLE 32

7-Chloro-4-(4-chloro-N-methylanilino)quinazoline (Compound No. 67)

2.5 g of 4,7-dichloroquinazoline and 2.2 g of *p*-chloro-*N*-methylaniline were added to 10 ml of ethanol and then the mixture was heated. The mixture became a homogeneous solution which solidified soon after. After cooling, the solidified crystals were collected and recrystallized from ethanol to give the desired compound in the form of its hydrochloride (Compound No. 68). The crystals of hydrochloride were crushed and added to a dilute aqueous solution of sodium hydroxide, with stirring, to precipitate the free base. The precipitate was collected by filtration, washed with water and recrystallized from ethanol to give 2.4 g (yield 65%) of the desired Compound No. 67 in the form of colourless plates melting at 129 - 131°C.

Elemental Analysis:

Calculated for $C_{15}H_{11}N_3Cl_2$:
C, 59.40%; H, 3.63%; N, 13.86%.

Found: c, 59.10%; H, 4.00%; N, 13.86%.

EXAMPLES 33 - 40

Following the procedures of Examples 31 and 32, the compounds listed in Table 6 were obtained; the

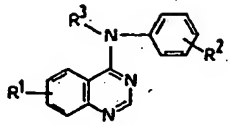
compounds are identified in the Table by the numbers heretofore assigned to them.

TABLE 6

Ex. No.	Cpd. No.	Melting point	Appearance	Yield
33	55	103 - 105°C	colourless granules	65%
34	61	118 - 120°C	colourless flakes	42%
35	63	130 - 132°C	colourless plates	33%
36	65	124 - 126°C	colourless needles	37%
37	69	82 - 85°C	colourless granules	10%
38	75	122 - 124°C	colourless granules	36%
39	77	135 - 137°C	pale yellow plates	51%
40	79	110 - 112°C	yellow needles	88%

CLAIMS

1. Compounds of formula (I):



(I)

in which:

R^1 represents a hydrogen atom, a halogen atom, a trifluoromethyl group or a nitro group;

R^2 represents a hydrogen atom, an alkyl group, an alkoxy group or a halogen atom; and

R^3 represents a hydrogen atom or an alkyl group;

provided that R^1 does not represent a hydrogen atom or a chlorine atom in the 6- position when R^2 and R^3 both represent hydrogen atoms;

and pharmacologically acceptable acid addition salts thereof.

2. Compounds according to Claim 1, in which R^2 represents an alkyl group or an alkoxy group having from 1 to 4 carbon atoms.

3. Compounds according to Claim 1 or Claim 2, in which R^3 represents an alkyl group having from 1 to 4 carbon atoms.

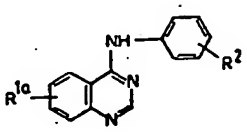
4. Compounds according to Claim 3, in which:

R^1 represents a hydrogen atom, or it represents a chlorine atom, a trifluoromethyl group or a nitro group at the 7- or 8- position;

R^2 represents a hydrogen atom or it represents a methyl group, an ethyl group, a methoxy group, an ethoxy group or a chlorine atom at the 4'- position; and

R^3 represents a methyl group or an ethyl group..

5. Compounds of formula (Ia):



(Ia)

in which:
R^{1a} represents a halogen atom or a trifluoromethyl group; and
R^2 is as defined in Claim 1 or Claim 2;
provided that R^{1a} does not represent a chlorine atom in the 6- position when R^2 represents a hydrogen atom; and pharmacologically acceptable acid addition salts thereof.

6. Compounds according to Claim 5, in which R^{1a} represents a halogen atom at the 7- position or a trifluoromethyl group at the 7- or 8- position.

7. Compounds according to Claim 5, in which:
R^{1a} represents a chlorine atom at the 7- position or a trifluoromethyl group at the 7- or 8- position; and
R^2 represents a hydrogen atom, a methyl group, a methoxy group or a chlorine atom.

8. Compounds according to any one of the preceding Claims, in which said acid addition salt is the hydrochloride.

9. 4-Anilino-7-chloroquinazoline and pharmaceutically acceptable acid addition salts thereof.

10. 4-Anilino-7-chloroquinazoline hydrochloride.

11. 4-Anilino-7-trifluoromethylquinazoline and pharmaceutically acceptable acid addition salts thereof.

12. 4-Anilino-7-trifluoromethylquinazoline hydrochloride.

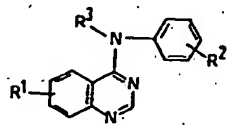
13. 7-Chloro-4-(*N*-methylanilino)quinazoline and pharmaceutically acceptable acid addition salts thereof.

14. 7-Chloro-4-(*N*-methylanilino)quinazoline hydrochloride.

15. 4-(*N*-Methylanilino)-7-trifluoromethylquinazoline and pharmaceutically acceptable acid addition salts thereof.

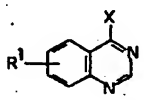
16. 4-(*N*-Methylanilino)-7-trifluoromethylquinazoline hydrochloride.

17. A process for preparing a compound of formula (I):



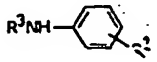
(I)

(in which:
R^1 represents a hydrogen atom, a halogen atom, a trifluoromethyl group or a nitro group;
R^2 represent a hydrogen atom, an alkyl group, an alkoxy group or a halogen atom; and
R^3 represents a hydrogen atom or an alkyl group);
or a pharmaceutically acceptable acid addition salt thereof,
which process comprises heating a haloquinazoline derivative of general formula (II):



(II)

(in which R^1 is as defined above and X represents a halogen atom) with aniline or an aniline derivative of general formula (III):



(III)

(in which R^2 and R^3 are as defined above).

18. A process according to Claim 17, applied to the production of a compound according to any one of Claims 2 to 16.

19. A process according to Claim 17 or Claim 18, effected in the presence of an inert solvent.

20. A process according to any one of Claims 17, 18 and 19, effected in the presence of an acid binding agent.

21. A process according to Claim 20 in which said acid binding agent is triethylamine.

22. A process according to Claim 17, substantially as hereinbefore described with reference to any one of foregoing Examples 1 to 26.

23. A process according to Claim 17, substantially as hereinbefore described with reference to any one of foregoing Examples 27 to 40.

24. Compounds of formula (I) and acid addition salts thereof when produced by a process according to any one of Claims 17 to 23.

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon Surrey, 1980.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.